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TECHNICAL PROGRESS AND PRODUCT MARKET SUCCESS IN PHARMACEUTICALS: THE CASE OF CHOLESTEROL ETHICAL DRUGS.

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November 1992 WP #3495-92 BPS

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Abstract

What is the role of a drug's technical performance as a driver of product market success? Are drug prices really rising as fast as they appear to? Are more expensive drugs really more effective? This paper uses cholesterol drugs to examine these questions. The results suggest that:

1) Quality adjusted prices are lower than the unadjusted ones—an annual increase of 6% compared to 9% when unadjusted for the years 1986 to 1992.

2) Expensive drugs tend to be more effective.

3) Technically superior drugs tend to be more successful in the market; the better the performance characteristics of a drug, the more successful it is in the market.

4) The technological generation from which a drug comes—a proxy for the characteristics of the drug—also has a significant effect on the drug's market success.

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Introduction

Ever since the advent of institutionalized corporate R&D, technology-intensive firms have invested significant percentages of their sales revenue on R&D in an effort to enhance or create new products or processes which they hope will help them gain or maintain a competitive advantage over their competitors. This has been particularly true of U.S. pharmaceutical firms which in the 1980s spent 15% of their revenues on R&D. But during that time, the same firms also spent about twice as much on sales and marketing as they did on R&D [Fortune, July 29, 1991]. Drug prices rose at 15.2% per year compared to a general inflation rate of 5.8% [Consumer Report, Feb. 1992] , while the return on equity for drug companies was 26% in 1990, twice the Fortune 500 median [Fortune, July 29, 1991]. To some policy-makers, these prices and profits seem rather large. Drug firms have argued that they need these profits in order to reinvest in R&D for better-performing drugs. Critiques of the industry charge that a lot of the R&D expenses go towards research for me-too drugs, that do not add much by way of innovation to the existing base of drugs.

All of this raises some very interesting questions. After taking into consideration the improving drug characteristics that are a direct result of the innovations that may be coming from the increasing R&D investment, are prices still rising that fast? In other words, what are the quality-adjusted price indexes for the drugs? Are more expensive drugs really more effective? Are technically superior drugs more successful in the market? Is it really worth a pharmaceutical firm's while to perform R&D for me-too drugs instead of investing the time and money in research for better-performing drugs? Since the goal of pharmaceutical research is to produce drugs that are as effective and safe as possible, and patients would prefer the most effective and safe drugs, shouldn't drug companies be spending more money on R&D than on sales and marketing?

These are very important questions that need to be addressed. The goal of this paper, however, is more modest. It looks at the first three questions and for cholesterol drugs only: First, the paper estimates the quality-adjusted price indexes for cholesterol drugs from 1986 to 1992. If these quality-adjusted prices are considerably lower than the unadjusted ones, then customers may be getting more for their money than it appears, and a possible reason for the improving drug performance characteristics that are responsible for the lower quality-adjusted prices may be investments in R&D[1].

Second, the paper looks at the role of a drug's effectiveness in explaining its price; i.e. see if more expensive drugs are really more effective. As explained later, this relationship cannot be taken for granted.

Finally, it examines the role of technical performance as a driver of market success in the cholesterol drug market. Technical performance here is proxied by drug performance characteristics and the technological generation (family) from which the drugs come. Performance characteristics make a good

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[1]Other possible sources of improvement in cholesterol drug performance include spillovers from the National Institutes of Health (NIH), other drug research projects, universities, and luck; all of which, arguably, are correlated with cholesterol drug R&D spending.

proxy because technical progress in pharmaceuticals usually results in enhancing or creating new drug characteristics. Technological generation is also a proxy for technical performance because some of the unmeasurable drug characteristics can be deduced from the drug's technological generation.

Market success in the paper is defined as the share of the number of prescriptions, and share of revenue that a drug captures.

The paper is organized as follows: Section I briefly examines the current literature on technological progress as a driver of product market success, and shows how this study contributes to that literature and to empirical work in pharmaceuticals. Section II provides a primer on cholesterol and what constitutes efficacy, safety, and compliance in cholesterol therapy. Both serve as the foundation for understanding most of what follows. Section III looks at the competing technological generations in the cholesterol drug market. Section IV briefly describes the price and market share equations that are the basis for the data analysis. Details of the econometric theory and model that are the basis of the analysis are given in Appendix A. Section V looks at the data, the rational behind their collection, and how they were collected. Finally, Section VI describes the data analysis and results while Section VII is a summary of findings, conclusions and a brief look at further work in this area.

Section I: Literature review and definition of the problem

The relationship between technical progress and commercial success is very complex. While CEOs and business scholars alike may be quick to point to technological innovation as the key driver of market success for some industries, they are not as quick to state exactly what its role is. Nor do they agree on what, in addition to or instead of technological innovation, drives market success. Technological innovation literature tends to concentrate on the idea that if firms are organized well [Burns and Stalker, 1961; Thompson,1967 ; and Woodward, 1965], communicate well [Allen, 1984], have the right individuals in the right roles [Roberts and Fusfeld,1982], and filter and process information optimally [Arrow,1964; Nelson and Winter, 1982; Henderson and Clark, 1990; Aoki, 1990], they will create new knowledge and generate technical ideas that lead to the right innovations for new or enhanced products or processes whose technical superiority will make them succeed in the market. To these scholars of innovation, while understanding and responding to customer needs is important, technical excellence is still the primary concern with the issue of, say, price being secondary.

Many economists, on the other hand, attribute commercial success primarily to quality-adjusted prices; i.e the price one pays for a product relative to its performance [Grilliches,1984; Berry, 1991; Trajtenberg, 1990]. Economists generally asume that product performance information is freely and readily available to rational customers who maximize their utility by making their choices. Economists also recognize the role of advertising as a driver of market success. Tirole (1988), for example, distinguishes between two views of advertising: the partial, and adverse views. The partial view admits that the assumption of perfect information is inappropriate and views advertsing as

providing the product information that customers can use to make their buying decisions. The adverse view holds that advertising persuades and fools consumers and creates product differentiation where it does not exist.

Marketing scholars believe that not only do product attributes and advertising play a critical role in the commerical success of a product, firm reputation, and marketing positioning may also be critical. For example, Urban et al [1986] found that the order of entry, time between entries, advertising and positioning effectiveness were significant in determining the market share of various brands of products.

Obviously, which driver of market success is important and what model (economists' or marketing) is appropriate for studying the relationship between technical progress and market success is a function of the kind of product in question and market it serves. Thus the market success of supercomputers, for example, is more dependent on its speed than is the success of aspirin on its performance, and for supercomputers, the technologists' assumption that technical excellence predominates may be appropriate for analyzing the drivers of succes.

In pharmameuticals, one would expect the relationship between technical progress and commercial success to be straight forward since the goal of pharmaceutical research is to produce drugs that are as effective and safe as possible, and therefore the most effective and safe drug should be the most successful in the market. That is, however, not always the case; and there are at least two schools of thought. One is that the raw performance of a drug as determined, say in clinical studies that are published in reputable medical journals, is what determines the market success of a drug [Avorn et al, 1982]. The drugs with the best such performance are those that will be the most successful in the market. Such a view suggests that to be successful in the market, one has to invest heavily in R&D—the main source of the innovations that give rise to high performing drugs. There is also no need for advertising, detailers, and product promotion since doctors read these reputable medical journals and can rationally choose the best drugs for their patients.

The other view is that the primary driver of a drug's market success is the benefits that doctors and their patients perceive as coming from the drug. So long as a drug meets the FDA's (Food and Drug Administration's) minimum efficacy and safety requirements, this view maintains, what matters is not its phamacological performance according to some clinical study but the benefits that doctors and patients perceive to be in the drug. Since the perception by doctors and patients of a drug's benefits is a function of performance and of advertising and promotion, the latter may actually play a bigger role in determining market success than the raw efficacy and saftey performance of the drug. This view is strongly opposed by doctors who insist that they choose drugs based on careful analysis of clinical studies that they read in medical journals and from medical conferences [Schwartz et al, 1989]. However, in a study of physician prescription practices, Schwartz et al (1989) found that the most common reason given by physicians for prescribing certain drugs was patient demand; and right next to patient demand was intentional use by physicians of the placebo effect. Avon et al (1982) also found that a physician's prescription habits were more likely to be influenced by colleagues than by what he/she read from medical

journals; colleagues that may have obtained their information from anywhere including advertising. For pharmaceutical products, then, technical progress, prices, advertising, firm reputation and entry order may all be drivers of market success.

Unfortunately, there is very little existing theoretical or empirical work on this important topic. Berndt, Griliches, and Rosett (1992) examined the price indexes for drugs. But these were not quality-adjusted price indexes. [On-going empirical work includes hedonics studies of some anti-hypertensive drugs by Berndt et al at MIT; hedonics of anti-ulcer drugs by Valery Suslow of the University of Michigan; and of market entry order effects of anti-ulcer drugs by G. Urban et al at MIT.]

This paper is part of this continued effort to learn more about the pharmaceuticals industry, through empirical work. Specifically, it examines three issues: 1) quality-adjusted prices, 2) the relationship between prices and drug performance on the one hand, and 3) that between technical performance and market share.

1) Quality-adjusted Prices:

The concept of quality-adjusted prices is best illustrated with an example. If you bought a Macintosh SE personal computer in 1988, it is likely that you paid more than $2000 for it. Today, the same SE (now repackaged as the Macintosh Classic) costs about $1000. So, forgetting about inflation, one can say that the price of the SE has fallen by more than 50%. But the 1992 SE now also offers four times the main memory, four times the disk memory, a faster processor, an operating system that does more, and etc, etc; i.e. the performance attributes of this 1992 SE are better than those of the 1988 version. If one were to buy a personal computer with the attributes of the 1988 SE, one would pay even less than the $1000. Put differently, the quality-adjusted price of the Macintosh SE—the price that one would pay for the 1992 SE if it had the performance characteristics of the 1988 SE (i.e. if the computer's attributes had been held constant)—is even lower than the $1000.

Quality-adjusted prices allow one to see the effect of those product attributes that customers value (and indirectly, the R&D or other factors that enhance or create those performance attributes) on prices.

The prices of drugs rose an average of 15.2% (compared to an inflation rate of 5.8%) in the 1980s. When asked why they charge such high prices and make such high profits, drug firms argue that they need the profits to plough into R&D for future better-performing drugs. For a given market structure, the quality-adjusted prices of these drugs are a good measure of the effect of R&D or other drivers of product performance. If the quality-adjusted pices differ considerably from the unadjusted ones, then one cannot rule out the claim by drug firms that they are reinvesting drug profits in R&D for better performing drugs. A better measure of how fast the price of a product is rising or falling is the quality-adjusted price index of the product. It measures how much the customer is paying for the product, given the performance.

2) Drug Effectiveness and Prices:

It is not unusual to find drugs that deliver about the same effectiveness but at very different prices. A case in point is Genentech's TPA (Tissue Plasminogen Activator) that in 1990 cost $2,200 compared to SmithKline's Eminase at $1,700 and Hoechst's older Streptokinase at only $200 a dose, but they all delivered about the same effectiveness[2] [Businessweek, Aug. 13, 1990]. The drugs are used to disolve blood clots.

Firm reputation or brand name can also overshadow the efficacy (or lack of) of a drug when it comes to pricing. For example, a firm with a reputation for developing drugs for diseases of the central nervous system (CNS), may be able to get away with higher prices for an average-performing CNS drug than a firm just breaking into the CNS market that otherwise has a better-performing drug.

Some firms may also price drugs very highly, not so much because of their performance, but as a signal of how novel the product is or how the firm wants doctors to perceive the drug. Such cases are enough reason to include an examination of the relationship between effectiveness and price in empirical studies of drugs. One goal of this paper then is to see if expensive drugs do perform better.

3) Technical Performance and Markets Success:

The goal here is to see if better-performing drugs command a market share premium; and if so, what the role of each performance parameter is. For some of the reasons cited earlier, one cannot assume that the best performing drugs will command the highest market share. Some of the reasons cited earlier for certain drugs being priced higher than their performance would indicate also apply here. One can also expect brandname reputation to be important.

A major problem with such an analysis is the fact that the performance of most drugs is not easy to measure. For most of these drugs, there is no objective way of determining how effective they are. How does one tell by how much one ulcer drug is better than another? For cholesterol drugs, this is not as troublesome a problem. Their goal is to reduce the level of cholesterol in patients and reductions in cholesterol levels are measurable quantities (see the next section). So this paper examines how much of the variation in market share and prices is due to the performance characteristics of the drugs. But even with cholesterol, not all benefits of technical progress are measurable. Two examples help illustrate this: 1) Probucol's measured performance characteristics are not very flattering, but it is believed to retard artherosclerosis by antioxidant mechanisms not directly related to reductions in cholesterol [Goodman, A. G et al, 1990]; i.e. these drugs somehow "eat up" some of the material that usually builds up inside the blood vessels eventually clogging them. 2) Bile acid sequestrants are also generally believed to be safer since they work by combining with bile acids in the stomach, and don't get absorbed into the blood stream—a characteristic that is not easily measurable. (More on both in later sections.) An analysis that does not take these

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[2] TPA breaks clots most effectively but can cause bleeding. Eminase can be injected more easily and lasts longer; but side effects include hypotension. Streptokinase has more side effects.

unmeasurable, yet important, characteristics into consideration will underestimate the value of certain drugs. Therefore the technological generation from which a drug comes is also used as an independent variable in explaining variations in the price and market share of that drug.

Understanding the role of technical performance as a driver of market success is important for several reasons. First, it is important for firms to know exactly what the contribution of each of the technical characteristics of drugs is to price and/or market share. It is also helpful to know what price or market share premium each technological generation commands, when a firm wants to decide on what technological generation to pursue R&D in. Second, pharmaceutical firms have sometimes been accused of spending too much money on R&D for me-too drugs—drugs that are very closely related to and have very little or no performance advantage over existing drugs; money that could have been channelled towards programs for better-performing drugs. Therefore if one can show that the market values better-performing drugs, i.e show that superior drug characteristics and/or technological generation command a price and/or market share premiun, R&D resources could be diverted not only from me-too drugs, but also from advertising and promotion, to R&D for potentially better performing drugs. Instead of looking for just another calcium channel blocker, a firm would strive for one that performs significantly better than previous ones or better still find another technological generation with superior performance characteristics. Of course, the cost-effectiveness of the drug must still be determined.

Advertising and Promotion:

This version of the paper doesn't include the role of advertising and promotion in determining market success. As soon as such data are obtained from IMS, the paper will be revised.

Section II: Measuring Market Success in the Cholesterol Drug Market:

Cholesterol Primer:

To better understand this examination of technical progress as a driver of market success, it is worthwhile going over some background material on cholesterol and the goal of drug design to combat high levels of cholesterol.

With all the "no cholesterol", "low cholesterol" marketing labels on products these days, one might think that cholesterol is all bad. No, it isn't! It has several vital bodily functions: 1) It is the starting material for the synthesis of such key steroid hormones as progesterone, testosterone, corticosterone and aldosterone. 2) It is used to produce bile juices which are important in food digestion. 3) It is a key component in cell membranes. But too much of it could lead to atherosclerosis and the risk of coronary heart disease (CHD).

Cholesterol circulates in the body as a component of lipoproteins (proteins that are soluble in fat). These lipoproteins are composed of triglycerides and cholesterol, surrounded by apoproteins. The density of these lipoproteins is important. Low density lipoproteins (LDL) carry the so-called "bad" cholesterol. They contain about 70% of plasma cholesterol and have a relatively long half-life of 1.5 days. This gives the cholesterol in LDL a bigger chance of depositing on the

walls of blood vessels and eventually clogging them. High density lipoproteins (HDL) cholesterol, on the other hand helps transport LDL cholesterol from dying cell membranes back to the liver and extra-hepatic tissue for synthesis that require cholesterol, thus helping reduce the level of plasma cholesterol; and that's why HDL cholesterol is called "good" cholesterol.

Many major studies have established that the risk of coronary heart disease (CHD) is directly proportional to the level of plasma cholesterol, and the concentration of cholesterol in LDLs, while being inversely proportional to the concentration of HDL cholesterol. [see for example Kannel et al 1979; Carlson et al 1972; Gordon et al; Helsinki 1984; Rhoads et 1976].

The goal then is to try to decrease the total amount of cholesterol in the body (keep the total plasma level below 200 mg/dl), especially the LDL cholesterol, while raising the level of HDL cholesterol. In treating high levels of cholesterol, an increasingly popular goal is to get a big decrease in the ratio of LDL/HDL.

When the body needs cholesterol to produce more bile juices, form cell membranes or to synthesize steroid hormones, it gets it directly from diet, from plasma LDLs or the liver synthesizes it. Designing ethical drugs to combat high levels of cholesterol, then, focuses on three things: 1) Limiting the synthesis of cholesterol (these are the so-called HMG CoA reductase inhibitor drugs) 2) Accelerating the absorption of cholesterol from plasma by, for example, forcing the excretion of bile juices so that the liver has to get cholesterol from plasma in order to produce more juices (such drugs are the so-called bile acid sequestrants 3) limiting the absorption of cholesterol from the digestive system.(e.g bile acid sequestrants). The next section on technological generations treats more aspects of drug origins.

Increasingly, doctors also want to reduce the total plasma triglycerides in their patients.

Pharmaceutical drug Performance characteristics; efficacy, safety, and compliance.

A drug's performance is usually measured by three parameters: efficacy, safety and compliance. The efficacy of a drug is its ability to cure or prevent the illness, or alleviate the condition or symptom that it is designed to. In addition to being effective, the drug must also be safe. Clinical testing and FDA examinations are designed to assure that the drug is not only safe, but also effective in curing or alleviating the condition that it is designed to. But to be effective and safe, the drug must be such that patients can take it at the frequency and conditions prescribed. This is where compliance comes in. A drug's compliance is those characteristics of the drug that make it easy for patients to comply with their doctors directions on how to take the drug. Thus an antihypertensive drug that must be taken three times a day has less compliance than one that only has to be taken once. Adverse side effects also make a patient less likely to comply with the directions for taking the medication.

Some of the characteristics that determine efficacy, safety and compliance of cholesterol drugs are listed in the table below. (Their definitions are given either in Table 1 or Appendix D)

Efficacy	Safety	Compliance
- LDL	- Adverse effects	- Administration Freq
- Total-C	- Contraindications	- Adverse Effect
- HDL	- Tolerability	
- LDL/HDL		
- Total-C/HDL		
- Triglycerides		

[See Table 1 and Appendix D for definitions]

Section III: COMPETING TECHNOLOGICAL GENERATION:

As stated in Section I, using a drug's measurable performance characteristics alone to proxy the technical progress embodied in that drug may not do justice to the drug's technical performance because not all of a drug's desirable characteristics (perceived and otherwise) are measureable; not even for cholesterol drugs. Two examples were cited earlier to illustrate this: 1) Probucol's measured performance characteristics are not very flatering (it actually *reduces* HDL by 27% instead of increasing it), but it is believed to retard artherosclerosis by antioxidant mechanisms that are not directly related to cholesterol reduction [Goodman et al, 1990]—an unmeasurable characteristic that can help its market performance 2) Bile acid sequestrants are also generally believed to be safer since they work by combining with bile acids in the stomach and being secreted, and don't get absorbed into the blood stream. To pick up the effects of these unmeasurable characteristics, one has to turn to the underlying technology for these drugs. In this paper, a technological generation for pharmaceutical products is defined as a family of products with the same mechanism of action, and very similar molecular structure. Each member of the family is usually an improved version of the preceeding members, having benefitted from the technological advances made in their predecesor. The improvements in the characteristics of each generation are constrained by some physical limit, as the wavelength of light for photolithography equipment or the speed of light for uniprocessor supercomputers.

Members of each family tend to have very similar characteristics. For example, Fibrates are very good at reducing triglyceride levels and raising HDL levels but have a lackluster performance when it comes to reducing LDL or total plasma cholesterol levels (more on this later; but see figures 6d and 6a).

Products for combating high cholesterol levels come from five main technological generations: Chronologically, these are: 1) Nicotinic Acid, 2) Fibric Acids, 3) Bile Acid-binding resins (also called Bile Acid Sequestrants), 4) Probucol, and 5) HydroxylMethylGlutoryl co-enzyme A (HMG CoA) reductase inhibitors. Table 2 shows the products in each generation, introduction year, and

key performance characteristics. A brief description of each technological generation follows:

1) Nicotinic acid:

Although Nicotinic acid was first produced by oxidation back in 1867, and from natural sources in 1917 [Witiak, D. K et al, 1991] it was not until 1955 that its plasma lipid-lowering properties were discovered. (Nicotinic acid is the name reserved for the Niacin used for lipid-lowering applications). After all these years, however, the mechanism by which Nicotinic acid lowers plasma cholesterol is still not well known. It also has some serious side effects and does not dwell long in plasma [PDR, 1992]. Searches for analogs that overcome these problems have not been successful. Nicotinic acid remains the only member of this family.

2) Bile Acid-binding resins (also called Bile Acid Sequestrants)

Right after Nicotinic acid, came the Bile acid-binding resins. They reduce cholesterol levels indirectly: they bind to bile juices in the gastrointestinal tract, and are excreted. And since cholesterol is used to make bile juices, the body has to use up its stock of cholesterol in order to replace the excreted juices. The biggest advantage of these bile acid sequestrants is that they are not absorbed by the body, and are therefore relatively safe, with fewer serious side effects than Nicotinic acid.

Their origin stems from the observation back in 1953 that Ferric Chloride ($FeCl_3$) precipitated bile salts in vitro and lowered cholesterol levels in chickens with high cholesterol levels [Siperstein, M. D et al, 1953]. However, because of the toxicity of high levels of iron, cholestyramine, a Dow Chemical compound which contains no iron, was chosen for testing.

Although first tested as a cholesterol lowering drug, cholestylramine got FDA approval first for puritus, a condition in patients with elevated levels of plasma bile acid. FDA approval as a cholesterol drug came later in 1973. The other member of this family, Colestipol, followed years later. Until the arrival of HMG CoA reductase inhibitors in 1987, Questran (Bristol Myers' brand name for Cholestylramine) was second only to Gemfibrozil in cholesterol drug sales.

3) Fibric Acids (aryloxyisobuteric acids)

The use of Fibric acids as a cholesterol lowering drug is often attributed to Thorp and Waring's screening tests in rats that found that some aryloxyisobuteric acids reduced plasma concentrations of triglycerides and cholesterol [Thorp and Waring, 1962). This led to the discovery of clofibrate and years later, the other members of the family: Gemfibrozil, fenofibrate, bezafibrate, and Ciprofibrate. Until the arrival of Merck's Mevacor (an HMG CoA reductase inhibitor) Lopid (Parke Davies' brand name for Gemfibrozil) was the best-selling cholesterol drug in the U.S..

Although the fact that fibric acids reduce plasma cholesterol and triglyceride levels is well established, there is still some controversy as to just what the mechanism of action is.

4) Probucol:

Probucol's cholesterol-lowering capability was discovered in 1964, shortly after the discovery of Fibric acids. The exact mechanism by which it lowers the cholesterol is not well known although it has been hypothesized that it increases bile acid secretion and the factional catabolic rate of LDL. It has very little effect on triglycerides and actually lowers HDL cholesterol levels (an undesirable feature). But it is also believed to reduce artherosclerosis by antioxidant mechanisms that are not directly related to cholesterol reduction (i.e. it "eats up" some of the material that tends to build up in heart blood vessels). Probucol is the only FDA approved member of this family.

5) HydroxylMethylGlutoryl co-enzyme A (HMG CoA) reductase inhibitors:

The HMG CoA reductase inhibitors family of cholesterol drugs is the latest generation. Its beginnings start with Endo's 1976 pioneering work [Endo et al, 1976] at Sankyo, Japan, in which he and his colleagues isolated Mevastatin, the first HMG CoA reductase inhibitor, from cultures of Pinincillin. Because of toxicity concerns, Mevastatin never really took off as a product; but the structure of HMG CoA reductase inhibitors had been discovered. In 1980, Merck and Endo concurrently isolated Lovastatin. For a while Merck had to halt clinical tests on its lovastatin (Mevacor) because of unsubstantiated rumors (Valegos, 1990) that the Endo's compactin caused cancer in dogs. Several years later, the tests were restarted at the urging of several doctors who found the product to be very effective in lowering cholesterol levels in some of their patients. The rumors turned out to be just that--rumors, and Mevacor was FDA approved in 1987.

HMG CoA reductase inhibitors work by reducing the synthesis of cholesterol. The first step in the synthesis of cholesterol in the liver is the conversion of Acetyl CoA to Mevalonate by HMG CoA reductase. After a series of other processes, mevalonate is converted to cholesterol. [Figure 1 details the process by which cholesterol is synthesized.] Therefore if the action of HMG CoA reductase can be inhibited, the conversion of Acetyl CoA to Mevalonate can be reduced and the subsequent production of cholesterol curtailed. And that's just what the HMG CoA reductase inhibitors do. About 60% of the body's cholesterol is synthesized. Therefore if systhesis is inhibited, the body will pick-up more plasma LDL cholesterol by receptor-mediated endocytosis whenver it needs the cholesterol, thereby reducing the level of plasma cholesterol. The body fights back the inhibition of the HMG CoA by producing more of it, limiting reduction of synthesis to only about a third.

Mevacor, an HMG CoA reductase inhibitor introduced in the US market by Merck in 1987, has been very successfull, capturing 52% of the retail revenue market share by 1989. Two other members of this trajectory have been introduced: Zocor, a synthetic analogue of Lovastatin (Mevacor), also introduced by Merck, and Pravachol, a Sankyo (of Japan) discovery being marketed in the U.S. by Bristol Myers--Squibb. Both products were FDA-approved for use in the U.S. in 1991.

History of progress:

A look at Table 2 and especially Figures 6a to 6h shows that key performance characteristics have improved steadily over the years—from Nicotinic acid to HMG CoA reductase inhibitors. (More on these technological generations later.) It is worth noting here that each drug's performance characteristics are a function of the technological generation from which it comes, and more importantly, these generations embody certain characteristics that are not measurable.

Section IV: THE MODEL:

Appendix A details the model behind the relations shown below and used in section VI to analyze the cholesterol data. The first of these relationships is the Log-Log equation that relates the market share, S_i, of a drug, and its performance characteristics, price, firm and market characteristics, and the technological generation from which the drug comes:

$$\text{Log}_e(S_i) = \alpha_0 + \xi_1 DM_{fi} + \xi_1 DM_{ti} + \beta_k \text{Log}_e(Z_i) + \xi_2 \text{Log}_e P_i + \xi_4 \text{Log}_e M_i + \varepsilon_i$$

Equation 5

where

Z_i is a vector of drug performance characteristics $(z_1, z_2 \ldots z_n)$ of drug i that make up its efficacy, safey and compliance.

P_i is the price of drug i

ε_i is a random variable that for the moment, we assume is iid (identically and independently distributed).

M_i is the vector of marketing and sales characteristics of drug i

DM_{fi} is the dummy variables for the firm producing product i

DM_{ti} is the dummy variable for the technological generation from which i comes

α, ξ, χ, and γ are constants.

The second, sometimes called the price function, relates the price of a drug , P_i, to its characteristics, firm and market characteristics and the technological generation from which it comes.

$$\text{Log}_e (P_i) = \gamma_0 + \chi_1 DM_{fi} + \chi_2 DM_{ti} + \beta_k \text{Log}_e(Z_i) + \chi_4 \text{Log}_e M_i + \varepsilon_i \quad \text{Equ. 6}$$

where the variables are as defined above.

Equation 6 can be estimated using OLS (Ordinary Least Squares) since none of the right hand variables is endogenous. Estimates of price from this equation can then be used to solve equation 5. This is the TSLS (Two Stage Least Squares).

Section V: THE DATA: Description and collection methods.

Two kinds of data, each with an entirely different collection method, were used: Drug performance characteristics data, and price and market share data.

Drug Performance characteristics:

Before collecting the data on the performance characteristics of drugs, three decisions had to be made: 1) which performance characteristics to include in the study, 2) what products to include in the study, and 3) which clinical studies would provide data that best represented the true performance characteristics of the drugs.

Which characteristics?

The performance characteristics variables for the study were chosen only after: i) carefully studying a sample of clinical studies on cholesterol therapy and noting the key performance variables for cholesterol drugs, ii) samplying advertisements for cholesterol drugs in *The American Journal of Cardiology, New England Journal of Medicine, Journal of American Medical Association,* and *Circulation* for the product characteristics the studies emphasized. The decision on what characteristics to include in the study was based on these two sources and brief consultations with a physician.

Which Products?

The data was collected on all the cholesterol drugs approved by the FDA and sold in the United States that are listed in at least one of the following medical or pharmaceutical reference publications: *Physician's Desk Reference (PDR) Manual, 1992; American Hospitals Formulary Service (AHFS), 1991; Drugs Comparisons and Facts, 1992; Drug Evaluations, 1990;* and *Goodman and Gilman's Pharmacological Basis for Therapeutics, Eighth edition.*

Which clinical studies are the best source of the data? Those that are stong on internal validity.

The choice of clinical studies from which to collect the data was the most critical part of the data collection process. The goal was to choose studies whose designs were strong on internal and external validity.

Internal validity:

The internal validity of a study is the extent to which any effects observed in subjects can be attributed to the treatment which the subjects received. The clinical studies chosen had to be designed and conducted in such a manner that any effects observed in subjects were attributable to the treatment the subjects got from the drug in question and not from something else. For example, each study had to be such that any decrease in cholesterol level observed must have been caused by the cholesterol drug and not a sudden change in, say, diet.

Clinical studies that are strong on internal validity are designed so that i) subjects are randomly assigned to the different treatment groups, ii) there is a group of subjects that gets placebo instead of the drug in question. This is the "control" for the study, iii) the studies are double-blind. Both doctors and patients don't know who is taking the medication and who is taking the placebo, and iv) the studies are conducted in parallel at multi-centers.

The National Library of Medicine MEDLINE database was searched for all the clinical studies on cholesterol drugs whose design had the elements of *placebo, double-blind, randomized, and multi-center or parallel.* This search provided only the abstracts to the studies. The relevant drug performance characteristics values were obtained from the medical journal articles. Most of the articles were from key medical journals like the *American Journal of Cardiology, New Eng. J. of Medicine, American Journal of Medicine, Circulation, Annals of Internal Medicine, Archives of Internal Medicine, American College of Cardiology, Journal of American Medical Association, Atherosclerosis and Angiology.* (See the references of Appendix C)

(Note: For Dextrothyroxine, there was no MEDLINE study conducted in parallel or at multicenters, and so only the other qualifiers apply to it).

External validity:.

The external validity of a study is the extent to which the results obtained from the study's sample can be generalized to the population from which the sample was drawn. The subjects for most clinical studies do not represent the U.S. population. They are mostly male, with very few minorities. So these results can be generalized only to a portion of the U.S. population. In collecting the data, there was not much that could be done to mitigate this particular external validity problem.

Non-clinical performance data like the frequency of drug administration, product introduction date, etc were obtained from the following: *American Hospitals Formulary Service (AHFS), 1991; Drugs Comparisons and Facts, 1992; The Merck Index, Eleventh edition; Goodman and Gilman's Pharmacological Basis for Therapeutics, Eighth edition; Physician's Desk Reference (PDR) Manual, 1992.*

Market Data:

Revenue and prescription market share data were obtained from *Drug Topics* , data which the magazine obtained from Pharmaceutical Data Services. These market share values were for the retail market only.

Prices were from the pharmaceutical ***drug Red Book*** which publishes manufacturer's suggested wholesale prices (SWP) and suggested retail prices (SRP) at the beginning of every year and then follows that with updates. The prices used did not contain any updates. Moreover, since the data on suggested retail prices were very incomplete, only suggested wholesale prices were used in the estimations that follow.

Section VI: MODEL ESTIMATION: Results and discussions.

The goal of this section is to use the data collected to 1) estimate the quality-adjusted price indexes, 2) examine how much of the variation in drug prices can be explained by drug performance and the technological generation of the drugs, and 3) examine how much of the variation in a drug's market share can be explained by its performance characteristics and the technological generation—for the latter two, find out if better-performing drugs and technological generations carry a price and market share premium. The section first looks at the improvements in each performance characteristic over the years—a measure of technical progress in cholesterol drugs. This is followed by the estimation of quality-adjusted price indices for the drugs. Then it examines the progress of the different technological generations. Finally, it examines how much of the variation in prices and market share is attributable to performance characteristics and technological generations.

i) Some simple Descriptive Statistics:

Table 3 provides some elementary but interesting statistics:

Price: The price in this context is in 1991 dollars using a GDP deflator, and it is how much one has to pay per day for the benefit of the average performance characteristics of the drugs. This price appears to have fallen substantially only in 1987 following the introduction of clofibrate generics, but risen gradually later. But it should be noted that these prices have not been adjusted for quality yet.

Innovative activity: Table 4 shows the mean values of some key characteristics from 1986-1992. The performance characteristics of the products improved steadily from 1986 to 1992. In particular, the average (each year) of low density lipoprotein cholesterol (LDL-C), total plasma cholesterol (TOTAL-C), plasma triglycerides, and adminstration frequency fell during that period. The average high density lipoprotein cholesterol (HDL-C) has been rising while the ratio of LDL-C to HDL-c and TOTAL-C to HDL-C have been falling. But one has to interpret these numbers with caution. The characteristics of pharmaceutical products don't change; although the average changes because of new products with improved characteristics being introduced. Some of the "improvements" we see in

the table come from the introduction of generics or from manufacturers introducing different "packagings" (presentations) of already existing molecular elements.

Table 4 is a better indicator of innovative activity. It only shows the best value of each characteristic that was available each year. From the table, we can see the changes that occurred in 1988 following FDA approval of Merck's Mevacor in late 1987. The other changes appear in 1992 following FDA approval of Bristol Myers-Squibb's pravachol and Merck's Zocor both in December 1991. TOTAL-C , LDL-C/HDL-C,, TOTAL-C/HDL and drug administration frequency all improved.

ii) **Quality-adjusted price indexes (Table 5):**

The estimated quality-adjusted price indexes for the years 1986 to 1992 for the cholesterol drugs are shown in Table 5 (with 1986 as the base year). The values for 1987 should be interpreted with some caution since the coefficient for the 1987 dummy variable (D87) is significant only to 15.4%. It would appear that the quality-adjusted prices have not been rising as fast as the unadjusted values (an annual growth rate of 6% compared to an unadjusted value of 9%). The fact that quality adjusted annual price growth for that period is 33% lower than the unadjusted value, indicates that the drugs that were introduced during that period offered improving price-performance values.

iii) Technological Generations:

Figures 6a, 6b, 6c, 6d,6e, 6f, 6g and 6h show the performance of the different technological generations over the years for each of the key drug performance characteristics. We note two key trends: 1) within each technological generation, the key performance characteristics— low density lipoprotein cholesterol (LDL-C), total plasma cholesterol (TOTAL-C), plasma triglycerides, adminstration frequency, high density lipoprotein cholesterol (HDL-C), LDL-C/HDL-c and TOTAL-C/HDL-C—have, on the average, improved from one member of the family to the other. 2) Each technological generation that has been introduced, has on the average, performed better than previous ones.

The HMG CoA reductase inhibitors, from the latest technological generation, lead in all the key measurable performance characteristics (decrease in LDL, total plasma cholesterol, LDL/HDL ratio, TotalC/HDL ratio, administration frequency, and increase in HDL) except decrease in triglycerides where the fibrates are king. The HMG CoA's also have the fewest side effects. Thus, if the performance of a drug and/ or the technological generation from which it comes matters, we can expect HMG CoA reductase inhibitors to carry a price and market share premium.

Merck's simvastatin which is a synthetic analogue of lovastatin shows considerable performance improvements over the latter. Bristol Meyers-Squibb's recently introduced pravastatin lags even lovastatin in most categories except administration freqency. This is a me-too drug.

iva) Prices: Do better performing drugs carry a price premium?

The effects of performance, and technological generation of drugs on price is estimated using equation 6. Table 1 details the construction of the variables used in this equation.

Results: (Refer to Table 6a)

The data used to generate the results of Table 6 are the panel data described earlier and are for the years 1986 to 1992. There were 309 observations over that period.

The negative and highly significant coefficients of LogTOTALC and LogLDL supports the hypothesis that drugs that lower total plasma cholesterol and/or low density lipoprotein (LDL) cholesterol command a price premium (all else equal). LogHDL is positive and significant also supporting the belief by some that drugs that raise high density lipoprotein (HDL) cholesterol are valued by customers. LogADMIN and LogADVER are also negative and highly significant, pointing to the fact that the lower the administration frequency (the number of times the drug has to be taken each day) the better, and the fewer the number of adverse effects associated with the drug, the more desirable.

The coefficients of logLDL/HDL-- log of the ratio of LDL cholesterol to HDL cholesterol (LDL/HDL) --, and Log(TOTALC/HDL)—log of the ratio of total plasma cholesterol (TOTALC) to HDL cholesterol—were both negative and highly significant. Again, this is what was expected because the more a drug can decrease LDL or total plasma cholesterol while at the same time increasing the level of HDL cholesterol, the better the drug is. It should be noted that LDL, TOTALC, LDL/HDL and TOTALC/HDL were highly correlated and as Table 6 shows, each had to be run in a separate regression.

All of the above support the hypothesis that drugs with superior performance characteristics command a price premium

The other variables worthy of explanation in Table 6a are LogPKGEFF and GENERIC. The former is the log of the number of daily doses of each drug that come in the "bottle" of drugs bought. The negative and highly significant coefficient represents the fact that the more doses one can get in each bottle, the less the per dose cost. GENERIC is a dummy variable that is 1 if the drug is a generic and 0 otherwise. As expected, this coefficient is significant and negative. So some customers pay more for brand name drugs that provide the same performance characteristics as generics. Grilliches [1992] found that when a generic drug is introduced, while the market share for the brandname falls, the price sometimes actually rises taking advantage of, among other things, the inelastic taste of these customers.

Finally, LogTRIG stands for the log of the changes in triglyceride levels. Its coefficient is not significant in equations 1, 2 and 3 of Table 6a, but positive and significant in equation 4. It is expected to be significant and negative since the more a drug reduces the levels of triglycerides, the better.

ivb) Effects of technogical trajectories and firm reputation on price

Table 6b shows the effects of technological generation on price. The generations explain the variation in prices better than the performance

characteristics. The former have an adjusted R^2 of .807 versus .74 for performance characteristics alone. As pointed out earlier, this is expected because each drug has some unmeasurable characteristics that are best proxied by the technological generation from which it comes. Nicotinic acid was used as the base for the technological generation dummies. The coefficient of HMG CoA reductase inhibitors is positive and highly significant (p=0.000) showing that this generation does indeed command a price premium. The PROBUCOL and FIBRATES coefficients are negative and significant indicating that these two generations do not carry any price premium compared to Nicotinic acid. The surprise is BILEACID which, despite its average performance characteristics has the reputation for being safe since it does not get absorbed into the blood stream, but has a negative coefficient. This coefficient is, however, not very significant.

With Rhone-Poulenc as the base, firm effects on price are shown in Table 6c. Merck, with its HMG CoA products, commands the highest price premium.

Multicollinearity:

At this point, one might ask why the technological generation and firm dummies were not included in the same regression equation as the performance characteristics. Such a combined regression was evaluated and as Table 6d illustrates the explanatory variables were highly intercorrelated resulting in multicollinearity problems. In that table, many of the tolerances are very close to zero. The tolerance of an explanatory variable here is defined as one minus the squared multiple correlation between that variable and the remaining explanatory variables. If there is no correlation at all, the tolerance is one. If there is high correlation, as is the case here, the tolerance is close to zero. The tolerance values, provided by the SYSTAT computer program that was used for all the regressions in this paper, were used to screen for this multicollinearity in all the regressions.

Appendix B outlines some of the reasons why the data used in this paper, and most drug characteristics data, may be more prone to multicollinearity.

v) MARKET SHARE.

a) Effect of performance characteristics

Before getting to the analysis, a note about the data is in order. Market share data were available only for the retail market for the years 1987 to 1991. The data didn't include any prices and so the wholesale prices from the *Drug Red Book* were used. Additionally the market shares were not by presentation. This resulted in only 25 observations.

Now the analysis: Two kinds of marketshare are examined here: share of the number of prescriptions, and share of revenue.

Both equations 5 and 6 are used in the estimation of what determines market share. Equation 6 is used to get estimates of the variable DPRICE (deflated price) which is then used as an instrument in the two stage least squares (TSLS) estimation of LogRXSHARE and LogRVSHARE (log of market share—number of prescriptions, and Log of market share—revenue respectively). Tables 8a and 10 display the results.

For both logRXSHARE and LogRVSHARE, the coefficients of LogTOTALC, and LogTrig are significant (the former only to a 15% level of

significant) and negative supporting the fact that the drugs with large market shares are those that perform better when it comes to lowering cholesterol and triglyceride levels. In both OLS and TSLS versions, the price was not significant in determining market share.

Again, as explained earlier, multicollinearity limited the number of variables that could be included in the evaluation. This was particularly so for the market evaluation where only 25 observations were available—data on five drugs over a five year period. Appendix B goes into more details why this data is more prone to multicollinearity. Because of this problem, only two explanatory variables—LogTOTALC, and LogTrig—were included in the equation. For the same reasons, firm and technological generation dummies could not be included in the same equation either.

b)Effect of technological generations

Table 9 shows the effect of technological generations on market share. As was the case with prices, the generations actually explain more of the variation in market share than do the performance characteristics, again indicating that some of the the characteristics that customers value are not measurable but are associated with technological generations by doctors and their patients. The adjusted R^2, when the independent variables are measured performance characteristics is .39 compared to .506 when the independent variables are the generations. With PROBUCOL as the base technology, HMGCoA and FIBRATES are both positive and highly significant, again indicating that these relatively better-performing trajectories command some market share premium. The coefficient of BILEACID is not significant.

Missing Variable:

As stated earlier, drug advertising and promotion data were not available and therefore not included in the analysis. There are two possible effects that these missing variables could have on the coefficients obtained. If drug companies spent a lot more money on advertsing drugs with superior performance characteristics, then the estimates of the coefficients of these performance variables obtained in the analysis would be higher than they ought to be. If on the other hand, these firms spent more on drugs on lackluster performance in an effort to compensate for the lack of performance, then the coefficients obtained are really better than they look.

As pointed out earlier, most economics-based analysis of the effects of product attributes on market performance don't include advertising or promotion expenditures.

SUMMARY, IMPLICATIONS and CONCLUSIONS:

The paper set out to do three things: 1) Estimate the quality-adjusted price indexes for cholesterol drugs from 1986 to 1992. The idea was that if these quality adjusted prices were considerably different from the unadjusted ones, then one cannot dismiss the arguement of drug firms that they are pumping profits into R&D for better drug characteristics. 2) See if drugs with higher prices perform

technically better. i.e. see if better-performaing drugs command a price premium. 3) Find out if better-performing drugs command a market share premium. Technical progress was proxied by drug performance characteristics, and technological generations. Market success was proxied by market share (both number of prescriptions as well as the revenue).

Using data from the cholesterol drug industry, the paper showed that drug quality-adjusted prices from 1986 to 1992 grew at an annual rate of 6% compared to an unadjusted value of 9%, and that highly priced drugs are also more effective. It also showed that a drug's performance does indeed explain most of the variation in the drug's price and market share; so does the technological generation from which it comes. In particular, a cholesterol drug's ability to i) reduce the total amount of plasma cholesterol, ii) decrease the level of low density lipoprotein (LDL) cholesterol iii) increase high density lipoprotein (HDL) cholesterol (so-called good cholesterol), and vi) decrease the ratio of total plasma cholesterol to HDL—explains most of the variation in prices and to a less extent, market share. Lower administration frequency and adverse reactions also pay. The technological generation from which a drug comes—a proxy for unmeasured characteristics of the drug—also explains most of the variation in the price and market share of the drug.

The implications are that if a firm is interested in a price premium and/or larger market share, it may be better off chanelling its resources towards R&D that would lead to better performing drugs (from a better performing trajectory) than allocating those resources to me-too drugs with lackluster performance; that is if the incremental cost of getting that extra unit of performance does not overwhelm the extra price and market share that is gained as a result of the incremental performance.

Finally, the technological generations show a very encouraging trend: Within each technological generation, the key performance characteristics have, on the average, improved from one member of the family to the next. Between generations, each technological generation that has been introduced, has on the average, performed better than previous ones.

Further work:

The difference between quality-adjusted and unadjusted price growth shows that the price-performance of drugs being introduced in the market is getting better. There may be several reasons for this continued improvements in drug performance. One obvious one is the R&D investments by drug companies. But there are alternate possibilities: spillovers from the NIH or non-cholesterol research. An obvious area of research then would be to try and locate the source of causality for the improving characteristics; see if it is really the investments in R&D by drug firms.

The data analyzed so far have been on cholesterol. A similar analysis is needed for other cardiovascular drugs. Such an analysis should also contain sales expenditures on advertising, promotion and detailing. Market share data by presentation for the wholesale market should also be included.

Additionally, it would be interesting to see what the effect of market entry order is for the cholesterol market.

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Table1: Variable Construction:

LogDPRICE	Log of the daily cost of the drug. Deflated to 1991 dollars.
LogPKGEFF	Log of Pkgeff where Pkgeff is the number of doses that come in a "bottle" of the drug. This is to pick up the effect of the fact that the per dose cost of a drug that comes 500 tablets per bottle or package is less than that of one that comes 50 tablets per bottle.
LogADMIN	Log of the administration Frequency. i.e how often one has to take the drug each day
LogLDL	Log of the change in Low Density Lipoprotein (LDL) cholesterol that comes from taking the drug
LogHDL	Log of the change in High Density Lipoprotein (HDL) cholesterol that comes from taking the drug.
LogTOTALC	Log of the total change in plasma cholesterol that comes from taking the drug.
LogTRIG	Log of the change in plasma triglycerides that comes from taking the drug
LogLDL/HDL	Log of the change in the ratio of Low Density Lipoprotein (LDL) cholesterol to high density lipoprotein (HDL) cholesterol that comes from taking the drug
LogTOTC/HDL	Log of the change in the ratio of total plasma cholesterol to high density lipoprotein (HDL) cholesterol that comes from taking the drug
Log ADVER	log of the number of the average number of adverse reactions.
GENERIC	Dummy variable that is 1 if the drug is a generic and 0 if not.
D92,D91,D90,D89, D88,D87	Dummy variables for 1992, 91, 90, 89, 88, 87 respectively
LogRXSHARE	Log of the market share for the number of Prescriptions (Rx)
LogRVSHARE	Log of the revenue market share.
LICENCE	1 if the drug was licensed; 0 if not
Generation Dummies	
HMGCoA	1 if drug is of the HMGCoA reductase inhibitor generation; 0 if not.
FIBRATES	1 if drug is of the Fibrate generation; 0 if not.
BILEACID	1 if the drug is a bile acid sequestrant; 0 if not.
PROBUCOL	1 if the drug is Probucol; 0 if not.
Firm Dummies:	
MERCK	1 if Merck; 0 otherwise
UPJOHN	1 if Upjoh; 0 otherwise
PARKE_DAVIS	1 if Parke Davis; 0 otherwise
MARRION_DOW	1 if Marion Merrel Dow; 0 otherwise
BRISTOL_MYERS	1 if Bristol Meyers-Squibb; 0 otherwise
BOOTS_FLINT	1 if Boots Flint; 0 otherwise
WYETH_AYERST	Wyeth Ayerst; 0 otherwise

Generic Name	Brand Name	Firm	Year	LDL-C (%)	TOTAL-C (%)	Triglycerides (%)	HDL (%)	LDL/HDL (%)	TOTAL-C /HDL (%)	Admin Frep
1) Nicotinic Acid										
Nicotinic acid	Nicobid	Interstate		-18%	-13%	-7%	4%	-28%	-15%	3
	Niacin	Huffman-L		-18%	-13%	-7%	4%	-28%	-15%	3
	Nicolar	Rorer		-18%	-13%	-7%	4%	-28%	-15%	3
2) Bile Acid Binding Resins (Sequestrants)										
Cholestyramine	Questran	BMS	1973	-27%	-19%	17%	3%	-29%	-21%	3..5
Cholestyramine	Cholybar	Parke Davi	1988	-27%	-19%	17%	3%	-29%	-21%	3..5
Colestipol HCL	Colestid	Upjohn	1977	-27%	-19%	8%	4%	-29%	-23%	3
3) Fibric Acids (aryloxyisobutyric acids)										
Clofibrate	Atomid-S	Wyet-Ayerst	1965	-18%	-17%	-26%	7%	-24%	-21%	3
Gemfibrozil	Lopid	Parke Davi	1982	-13%	-12%	-42%	13%	-21%	-23%	2
4) Probucol										
Probucol	Lorelco	MMD	1977	-13%	-14%	1%	-27%	24%	21%	2
5) HMG CoA Reductase Inhibitors										
Lovastatin	Mevacor	Merck	1987	-34%	-26%	-15%	8%	-37%	-29%	2
Pravastatin	Pravachol	BMS	1991	-28%	-21%	-17%	8%	-36%	-30%	1
Simvastatin	Zocor	Merck	1991	-34%	-27%	-21%	12%	-45%	-27%	1
Other										
Dextrothyrozine	Chloxin	Boots Flint		-12%	-11%	-2%	-7%	-12%	-11%	3

Figure 2: The different Technological Generations of cholesterol drugs.

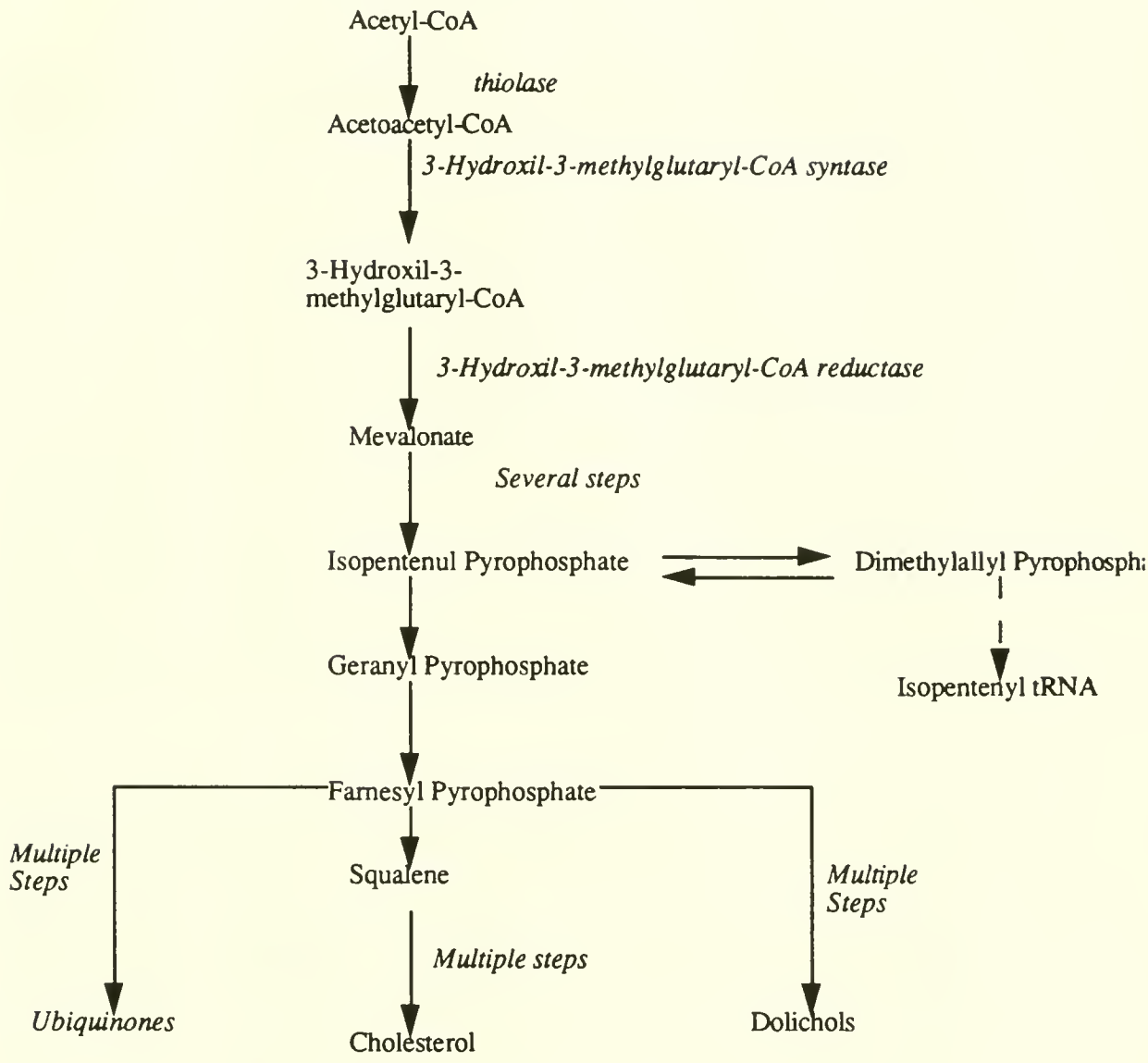


FIGURE 1. Key steps in cholesterol biosynthesis. *Adotped from Antilipidic Drugs by Witiak D. T et al 1991.*

Year	n	LDL-C (%)	TOTAL-C (%)	Trigly-cerides (%)	HDL (%)	LDL/HDL (%)	TOTAL-C /HDL (%)	Admin Freq	defla ted Price
1986	20	-17.25	-13.75	-5.65	0.1	-19.90	-14.50	2.33	1.74
1987	33	-17.82	-14.97	-12.06	2.63	-21.79	-16.94	3.03	1.56
1988	43	-18.40	-16.00	-16.47	3.91	-22.61	-18.49	2.98	1.55
1989	50	-18.86	-16.14	-14.14	3.46	-22.18	-18.04	2.98	1.89
1990	50	-18.86	-16.14	-14.14	3.46	-22.18	-18.04	2.98	1.89
1991	49	-19.65	-16.61	-14.78	4.33	-23.18	-18.84	2.76	2.13
1992	61	-22.16	-18.33	-15.53	5.44	-26.80	-20.67	2.56	2.71

Table 3: Mean Values key product characteristics from 1986-1992. See Table 1 for definition of terms.

Year	n	LDL-C (%)	TOTAL-C (%)	Triglyce rides	HDL (%)	LDL/ HDL (%)	TOTA-C /HDL (%)	Admin. Freq
1986	21	-27	-19	-42	13	-29	-23	2
1987	33	-27	-19	-42	13	-29	-23	2
1988	44	-34	-26	-42	13	-37	-29	2
1989	51	-34	-26	-42	13	-37	-29	2
1990	53	-34	-26	-42	13	-37	-29	2
1991	49	-34	-26	-42	13	-37	-29	2
1992	61	-34	-27	-42	13	-45	-30	1

Table 4: Best performance characteristics since 1986: Better indicator of technological progress?

Quality-Adjusted				Unadjusted Prices *	
Year	Estimated coefficient (t-value)	Price Index	% Change in Price Index	Price Index	% Change in Price Index
1986		1.000		1.00	
1987	.126 (1.429)	1.134	13%	1.09	9%
1988	.183 (2.133)	1.201	6%	1.19	9%
1989	.199 (2.370)	1.220	2%	1.24	5%
1990	.264 (3.171)	1.303	7%	1.42	14%
1991	.264 (3.103)	1.302	0%	1.55	9%
1992	.336 (3.987)	1.399	7%	1.70	10%
			Average quality adjusted= 6%		Average unadjusted = 9%

Table 5: Estimated quality-adjusted price indexes 1986-1992. Note that the 1987 coefficient is significant only to 15.4% . Values in parenthesis () are t-statics values. Annual % rise in quality-adjusted price index is 6% compared to 8% unadjusted.

* Uses only the cholesterol drugs that were present in the market in 1986.

Dependent Variable: LogDPRICE (Real Suggested whole sale Price in 1991 dollars)
n=309

	1	2	3	4
n = 309	Coef (t-value)	Coef(t-value)	Coef(t-val)	Coef (t-value)
Constant	2.339 (1.75)	3.333 (2.211)	3.004 (10.354)	3.819 (11.619)
LogPKGEFF (# of doses per bottle)	-.315 (-11.350)	-.314 (-11.40)	-.331 (-12.50)	-.324 (-12.04)
LogADMIN	-.243 (-2.246)	-.205 (-1.834)	-.192 (-2.313)	-.285 (-3.496)
LogLDL	-.355 (-2.246)	*	*	*
LogTOTALC	*	-.654 (-2.906)	*	*
LogLDL/HDL	*	*	-.338 (-4.497)	*
LogTOTC/HDL	*	*	*	-.443 (-4.239)
LogHDL	.275 (1.503)	.307 (1.787)	*	
LogTRIG	.085 (1.05)	.091 (1.188)	.097 (1.855)	.135 (2.53)
LogADVERS	-.188 (-2.443)	-.211 (-2.742)	-.103 (-1.243)	-.242 (-3.705)
GENERIC	-.770 (-12.019)	-.812 (-12.43)	-.828 (-12.43)	-.753 (-12.41)
D92	.336 (3.987)	.333 (3.966)	.346 (4.122)	.339 (4.033)
D91	.264 (3.103)	.267 (3.147)	.287 (3.387)	.267 (3.145)
D90	.264 (3.171)	.264 (3.184)	.279 (3.363)	.271 (3.260)
D89	.199 (2.370)	.198 (2.373)	.211 (2.532)	.203 (2.432)
D88	.183 (2.133)	.180 (2.130)	.194 (2.267)	.186 (2.179)
D87	.126 (1.429)	.126 (1.438)	.132 (1.498)	.127 (1.446)
F - ratio	84.99	85.640	100.357	98.211
Adjusted R^2	.780	.781	.780	.776

Table 6a: OLS regression. Effect of performance characteristics on price. Values in parenthesis () are t-statics values.
* Variables correlated with key variables and would cause multicollinearity problems if included.

Dependent Variable: LogDPRICE (Real Suggested whole sale Price in 1991 dollars) n=309

n = 309	Coef (t-value)	Standardized coefficient
Constant	2.07 (16.41)	0.00
LogPKGEFF (# of doses per bottle)	-0.42 (-15.66)	-0.50
GENERIC	-.81(-12.58)	-.61
HMGCoA	.57 (7.98)	.24
BileAcidSeq	-.15 (-2.31)	-.08
FIBRATES	-.23 (-3.62)	-.18
Probucol	-.41 (-4.43)	-.12
D92	.34 (4.5)	.21
D91	.297 (3.103)	.17
D90	.28 (3.59)	.16
D89	.199 (2.53)	.11
D88	.171 (2.13)	.09
D87	.136 (1.66)	.07
F - ratio	108	
Adjusted R^2	.807	

Table 6b: Effect of technological trajectories on price. Values in parenthesis () are t-statics values. 1986 is the base year, while NICOTINIC acid is the base trajectory.

Dependent Variable: LogDPRICE (Real Suggested whole sale Price in 1991 dollars)
n=309

n = 309	Coef (t-value)	Standardized coefficient
Constant	2.09 (17.73)	0.00
LogPKGEFF (# of doses per bottle)	-0.41 (-16.43)	-0.49
GENERIC	-1.09(-19.69)	-.82
BRISTOL_MYERS	-.09 (-1.17)	-.04
MARRION_DOW	-.47 (-4.71)	-.13
PARKE_DAVIS	-.15(-2.05)	-.18
WYETH_HERST	-.42 (-3.54)	-.10
UPJOHN	-.34 (-4.13)	-.13
BOOTS_FLINT	-.12(-1.63)	-.06
MERCK	.53(6.54)	.21
D92	.38 (4.5)	.23
D91	.29 (3.103)	.16
D90	.27 (3.59)	.15
D89	.19 (2.53)	.11
D88	.17 (2.13)	.09
D87	.14 (1.66)	.07
F - ratio	108	
Adjusted R^2	.807	

Table 6c: Firm effect on price. Values in parenthesis () are t-statics values. 1986 is the base year, while Rhone Poulenc is the base technological generation.

Dependent Variable: LogDPRIC

	Coefficient	Std Error	Tolerance	t-value	
Constant	31.86	10.91		2.9	
D92	.33	.078	.27	4.2	
D91	.29	.079	.31	3.7	
D90	.27	.077	.307	3.5	
D89	.19	.078	.319	2.5	
D88	.17	.079	.345	2.2	
D87	.14	.081	.41	1.7	
LogPKEF	-.94	.029	.49	-13.4	
LogAdmin	-.01	.119	.239	-.1	
LogLDL	-1.71	.716	.010	-2.4	
LogHDL	-4.87	1.84	.002	-2.6	
LogTRIG	-.57	.23	.018	-2.5	
Generic	-.7	.11	.09	-6.4	
HMGCOA	-.26	.415	.02	-.6	
Bileacid	-.29	.165	.07	-1.8	
FIBRATES	.6	.40	.006	1.5	
LogAdver	-.84	.296	.011	-2.9	
PROBUCOL	-3.46	1.184	.005	-2.9	

Table 6d: Technological generations and product characteristics.The very low tolerance values indicate multicolinearity in the explanatory variables.

Dependent Variable: LogRVSHARE n=25

	OLS		TLS	
	Coefficient	t-value	Coefficient	t- value
Constant	12.54	1.54	13.92	1.38
LogDPRICE	0.32	0.50	0.18	0.21
LogTOTALC	-3.19	-1.46	-3.57	-1.31
LogTrig	-1.13	-4.01	-1.13	-3.93
F - ratio	6.14		6.01	
Adjusted R^2	0.39		0.39	

Table 8a: OLS and Two-stage least squares estimation of effects of characteristics on revenue Market Share

Dependent Variable: LogRVSHARE n=25

	OLS	
	Coefficient (t-value)	Standardized coefficient
Constant	-2.74 (6.85)	0
HMGCoA	1.85 (3.26)	.59
BILEACID	-.404 (.024)	-.16
FRIBRATES	1.36 (2.39)	-.63
F - ratio	9.2	
Adjusted R^2	0.506	

Table 9: Effects of technological trajectories on revenue market share. Probucol is the base. (t-values in parenthesis)

Dependent Variable: LogRXSHARE n=25

	OLS		TSLS	
	Coefficient	t-value	Coefficient	t- value
Constant	2.12	0.271	1.07	0.11
LogTOTALC	-0.394	-0.19	-0.11	-0.04
LogDPRICE	0.85	1.39	0.96	1.13
LogTrig	-1.00	-3.71	-1.01	-3.65
F - ratio	5.0		4.67	
Adjusted R^2	0.33		0.32	

Table 10: OLS and Two-stage least squares estimation of the effects of performance characteristics on prescription market share.

Figure 6a: LDL cholesterol reduction

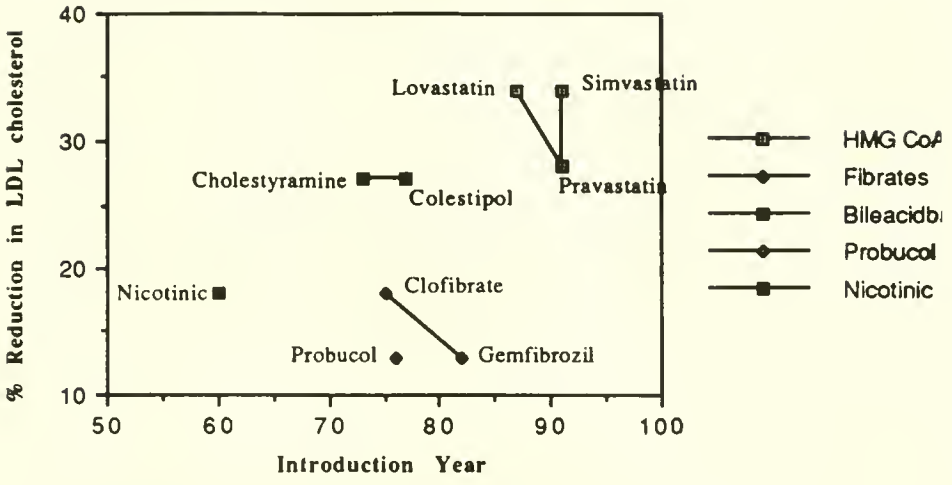


Figure 6b: Total Plasma cholesterol

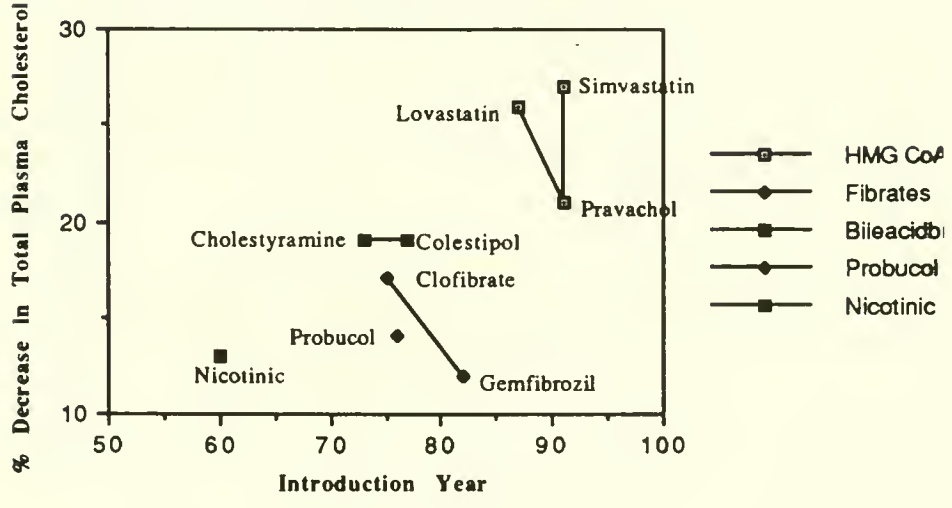


Figure 6c: HDL Increases

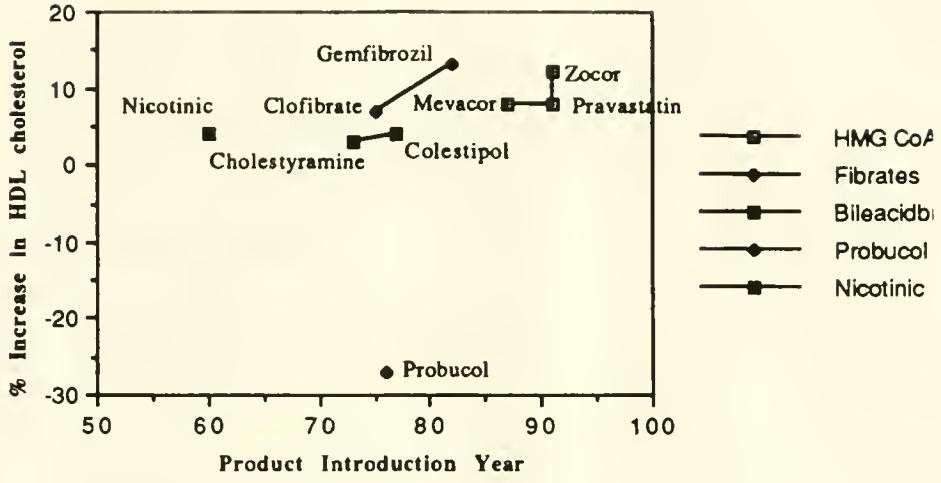


Figure 6d: Decreases in Triglyceride levels

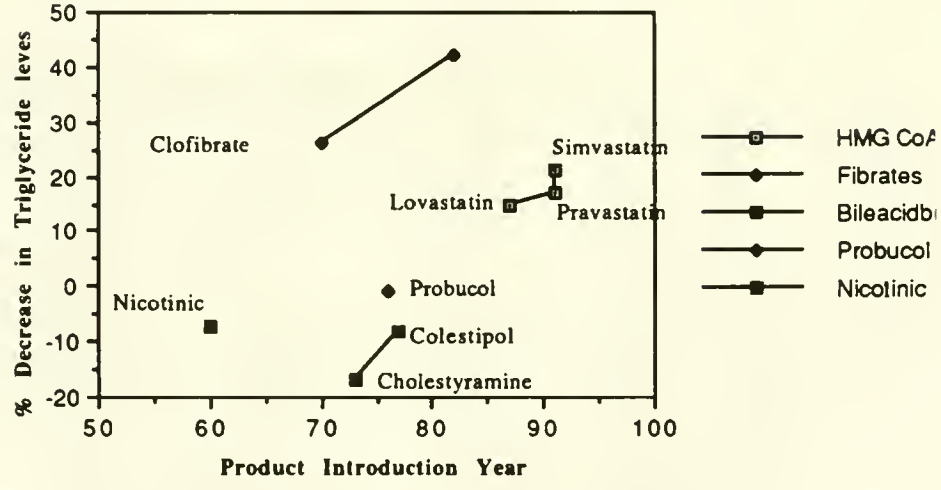


Figure 6e: Decrease in LDL/HDL ratio

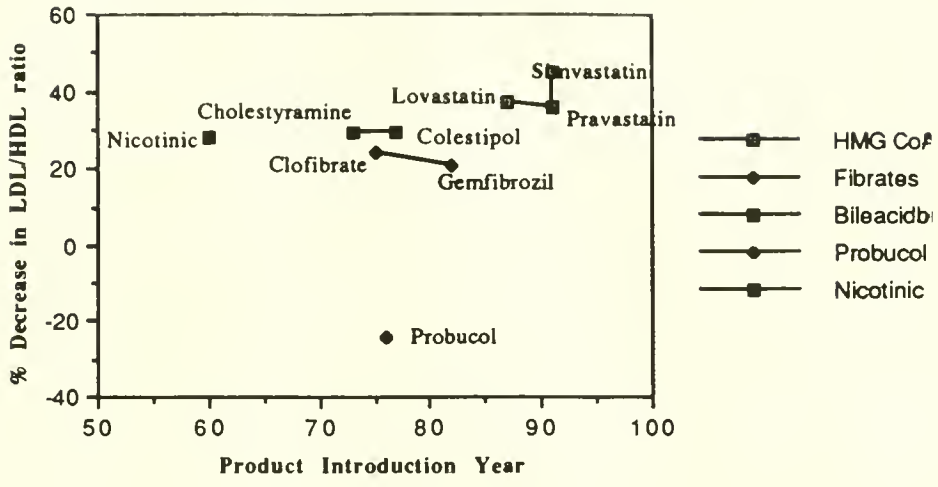


Figure 6f: Decrease in TotalC/HDL ratio

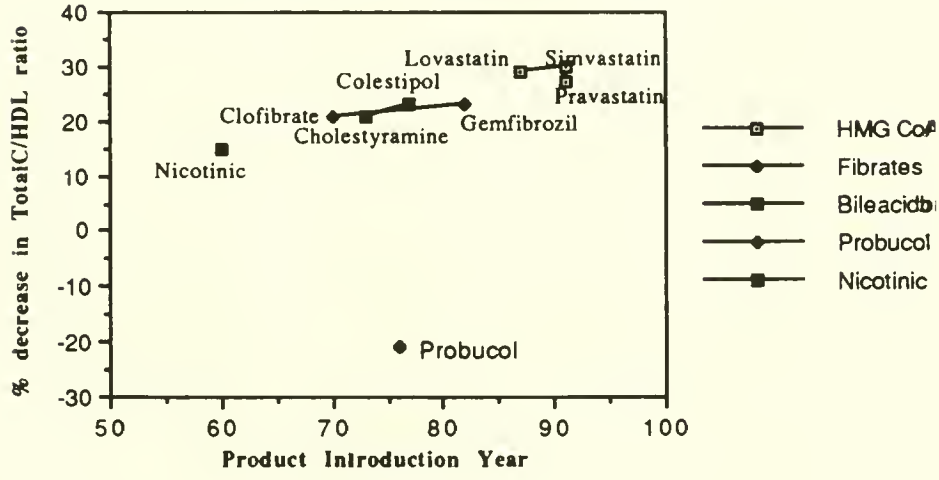


Figure 6g: Administration Frequency

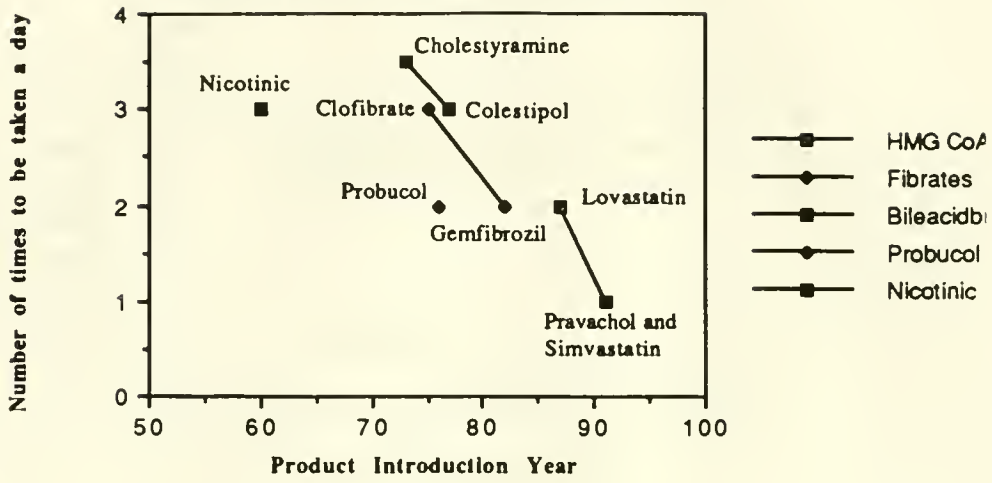
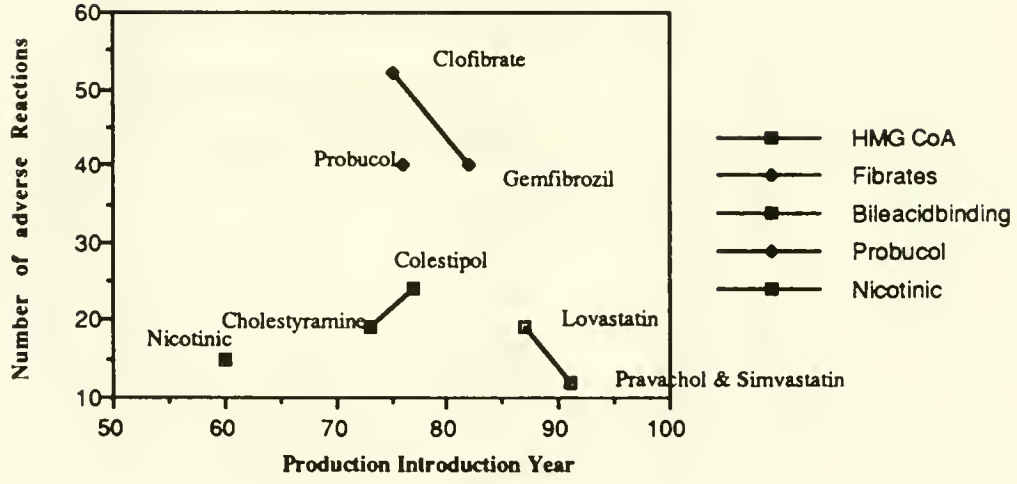


Figure 6h: Adverse Reactions



Appendix A: THE MODEL:

The Model:

One can view products as bundles of characteristics from which each consumer can choose that bundle that maximizes her utility; with each of these characteristics coming at a price--the hedonic price [see for example Griliches (1971), and Rosen(1974)].

The concept of hedonics has been used for everything from establishing quality-adjusted price indexes [see for example Griliches 1971, and Berndt 1991] to measuring product innovation [Trajtenberg 1990]. It is used in this paper to estimate the effect of technical innovation on market success.

Figure 1 shows the price-characteristics space on which both cost-minimizing producers and utility-maximizing customers locate. The price of a product p(z) is a function of the vector of the product characteristics $Z(z_1 \ldots z_n)$, and the customers' tastes which determine the value which the customers attach to the characteristics. (Note that only the plane in which z_1 varies is shown in figure 1.)

By using different technologies, cost-minimizing producers locate on different isoprofit curves $\Pi_1, \Pi_2 \ldots \Pi_c$. Utility-maximizing customers locate on indifference curves $U_1, U_2, \ldots U_n$. For each technology curve, improving the characteristics comes at increasing marginal costs. The locus of points where customers and producers are doing the best they can given what the others are doing is the price function, P(z). In other words, P(z) is the common tangent to the isoprofit and indifference utility curves; i.e the locus of points where marginal cost equals marginal utility. Thus

P = F(Z)Equation1

"Superconductance World":

Let us assume that we are in a world in which 1) Accurate, complete and detailed information on drug performance is freely and instantaneously available to doctors and patients so that there is no need for detailers (drug salespersons), advertising or other marketing/sales strategies, and such first-movers advantages as brand name 2) All doctors have the same characteristics and will all make the same choice given the same information. 3) Doctor's and their patients efficiently filter and process information from the patient's ailment and that from drug performance characteristics, and accurately choose an available drug whose characteristics just provide the patient with the best efficacy and safety that the patient can afford.

In such a world, the performance of a drug would be the sole determinant of it's price; and that price and the performance characteristics would be the determinant of the product's market share. Thus one would expect an antihypertensive drug that lowers blood pressure by 10 mm Hg to have a higher market share than one that only lowers it by 9.9 mm Hg if both deliver the same safety and compliance for the same price. In fact, such a drug should capture the whole antihypertensive market, all else equal. Drugs with the same characteristics would be perfect substitutes. Generics which normally carry a much lower price but are biochemically equivalent to brand names, should capture all the market share. Thus the characteristics of a drug--which are determined by the innovations that go into the drug--would be the sole determinants of the drug's market success.

Formally,

Let the utility (or wellness), U_{ji} of patient j who takes drug i, be

$$U_{ji} = \theta_d Z_i - \alpha P_i + \varepsilon_{ji}$$

where

Z_i is a vector of those characteristics ($z_1, z_2 \ldots z_n$) of drug i.that make up its efficacy, safey and compliance.

P_i is the price of drug i

ε_{ji} is a random variable that for the moment, we assume is iid (identically and independently distributed).

θ_d is the value that patient j 's doctor places on the vector of characteristics, Z_i, for drug i. This is the same for all doctors in this ideal world since they all have the same characteristics (training, read the same journals, etc).

The doctor will choose drug i over drug k for her patient if $U_{ji} > U_{jk}$ i.e if

$$\theta_d Z_i - \alpha P_i + \varepsilon_{ji} > \theta_d Z_k - \alpha P_k + \varepsilon_{jk}$$

Therefore the probability of drug i being chosen over drug k is

$$\text{Prob}(\theta_d Z_i - \alpha P_i + \varepsilon_{ji} > \theta_d Z_k - \alpha P_k + \varepsilon_{jk}) \text{ for all k.}$$

$$\text{Prob}(\varepsilon_{ji} - \varepsilon_{jk} > \theta_d Z_k - \alpha P_k - \theta_d Z_i + \alpha P_i)$$

This probability is i's market share, S_i and is given by

$$S_i = \int_A (\varepsilon_{ji} - \varepsilon_{jk}),$$

where $A = \theta_d Z_k - \alpha P_k - \theta_d Z_i + \alpha P_i$

Thus the market share will depend on the distribution of the error terms $\varepsilon_{ji} - \varepsilon_{jk}$ as well as the prices of the drugs, and drug characteristics.

"High Impedance world":

But we live in a world where despite all the efforts by the FDA, information about drugs may not be completely accurate. Nor is it freely and instantaneously available. Thus a firm's marketing and sales budget which determines how many detailers it can send out to deliver drug information to doctors and how much advertising to do, as well as a firm's brand name matter. The patient's and his

doctor's characteristics also matter, and more importantly, their perception of the characteristics of the drug. And this perception can be greatly influenced by other firm activities that have nothing to do with the performance of the product. Thus we can expect the firms market/sales strategy to play an important role even in pharmaceuticals where one would expect safety and efficacy to reign.

Formally, the superconductance model is modified to get the real life model as follows:

Let the utility (or wellness), U_{ji} of patient j who takes drug i, be

$$U_{ji} = \theta_d Z_i - \alpha P_i + M_i + T_i + \varepsilon_{ji}$$

where

Z_i is a vector of those characteristics $(z_1, z_2 \ldots z_n)$ of drug i.that make up its efficacy, safey and compliance.

P_i is the price of drug i

ε_{ji} is a random variable that for the moment, we assume is iid.

θ_d is the value that patient j 's doctor places on the vector of characteristics, Z_i, for drug i. This is a reflection of the doctor's characteristics that is in turn influenced not only by her patients, but also by the scientific journals that she reads, medical conferences that she attends, advertising, her colleagues and the detailers that call on her. $\theta_d = \theta_d(M_i)$

M_i is the vector of marketing and sales characteristics of drug i

T_i is the technological trajectory to which i belongs. It also encorporates the effects of doctors' and patients' perception of the trajectory. T_k is similarly defined.

The doctor will choose drug i over drug k for her patient if $U_{ji} > U_{jk}$ i.e if

$$\theta_d Z_i - \alpha P_i + T_i + M_i + \varepsilon_{ji} > \theta_d Z_k - \alpha P_k + T_k + M_k + \varepsilon_{jk}$$

Therefore the probability of drug i being chosen over drug k is

$$\text{Prob}(\theta_d Z_i - \alpha P_i + M_i + T_i + \varepsilon_{ji} > \theta_d Z_k - \alpha P_k + T_k + M_k + \varepsilon_{jk}) \text{ for all k.}$$

$$\text{Prob}(\varepsilon_{ji} - \varepsilon_{jk} > \theta_d Z_k - \alpha P_k + T_k + M_k - \theta_d Z_i + \alpha P_i - M_i - T_i)$$

This probability is i's market share, S_i and is given by

$$S_i = \int_A (\varepsilon_{ji} - \varepsilon_{jk}) \quad \text{Equations 3}$$

where $A = \theta_d Z_k - \alpha P_k + M_k + T_k - \theta_d Z_i + \alpha P_i - M_i + T_i$

Thus the market share will depend on the distribution of the error terms $e_{ji} - e_{jk}$ as before but now one's market strategy (number of detailers, sales and marketing spending), brand name, choice of technology, etc also matter.

The price of drug i is now also given by

$$P_i = f(Z_i, M_i, T_i, \theta) \quad \text{Equation 4}$$

A more rigorous version of equation 3 is considered below. But frequently the following simplified Log-Log version can provide useful results:

$$\text{Log}_e(S_i) = \alpha_0 + \xi_1 DM_f + \xi_1 DM_t + \beta_k \text{Log}_e(Z_i) + \xi_2 \text{Log}_e P_i + \xi_3 \text{Log}_e D_i + \xi_4 \text{Log}_e M_i \quad \text{Equation 5}$$

For estimation, the following log-log version of equation 4 is also used:

$$\text{Log}_e(P_i) = \gamma_0 + \chi_1 DM_f + \chi_2 DM_t + \beta_k \text{Log}_e(Z_i) + \chi_3 DM_o + \chi_4 \text{Log}_e M_i \quad \text{Equ. 6}$$

.where

DM_o is the dummy variable for "original discovery"; 1 if the firm was the first to discover the original molecular structure of the drug, and 0 if the firm licensed or me-too-engineered (reverse-engineered the drug.

DM_f and DM_t are dummy variables for the firm producing product i and the technological trajectory being used, respectively.

α, ξ, χ, and γ are constants. The other variables are as defined earlier.

.Equation 6 can be estimated using OLS. Estimates of price from this equation can then be used to solve equation 5. This is the TSLS.

MNL and Independence of irrelevancy alternatives problem

McFadden (1973) showed that if $\varepsilon_{ji} - \varepsilon_{jk}$ are independently and identically distributed (iid) with the Weilbull distribution, then Equation 3 becomes

$S_i = e^A/\Sigma_l e^A$ (l= 1 to L alternatives Equation 7

This the conditional logit model otherwise known as the multinomial logit (MNL) model in some circles. (where A is still as defined above)

The MNL model suffers from the independence of irrelevant alternatives (IIA) problem. From the multinomial logit of equation 7 it can be shown that for any j, the relative probability of choosing two alternatives is not affected by the presence of other alternatives. That is, the ratio S_i/S_j is independent of whether there are alternatives to choose from or not. This is the source of the IIA problem. This implies that if another product l with characteristics almost identical to i's is introduced, IIA dictates that the probability of choosing i remains S_i , instead of the expected close to $S_i/2$ value.

IIA also implies that cross-price elasticities for all alternatives are constrained to be the same (Berry, 1991). Thus although one would expect intra-technological cross-price elasticities to be closer than inter-trajectory, IIA forces all of them to be the same. It is this property that we will capitalize on. We will test the hypothesis that cross-price elasticities are the same within trajectories but different between trajectories. We go via the nested multinomial logit model (NMNL)

Nested Multinomial Logit Model (NMNL):

Probability of choosing drug d (which is in technological trajectory t) is given by

$S_{dt} = S_{d/t} \bullet S_t$ (e.g the prob. of choosing zocor)

where

$S_{d/t}$ = the prob. of choosing d given that it is in trajectory t (e.g prob. of choosing zocor given that we are in the HMG CoA cluster)

S_t = Prob. of choosing trajectory t (prob of choosing HMG CoA)

$S_{d/t} = \text{Exp}(bX_{dt}) / \Sigma_k \text{Exp}(\beta X_{kt})$ Equation 8 [for k (number of drugs in cluster t) from 1 to K]

where

X_{dt} is the vector product characteristics for drug d in cluster t.

$S_t = \text{Exp}(\eta_t(1-\xi)) / \Sigma_l \text{Exp}(\eta_l(1-\xi))$ Equation 9 [l= 1 to T, the number of trajectories]

where η_t is the inclusive value of trajectory t, and given by

$\eta_t = \text{Log}_e (\Sigma_k \text{Exp}(\beta X_{kt})$ Equation 10for all the drugs in trajectory t.

The key parameter here is ξ , the measure of substitutability between trajectories. If $\xi = 1$, then the drugs in the different trajectories are substitutes (high cross-price elasticities). If $\xi = 0$, then the trajectories are independent (price-wise).

To summarize the estimation process for the nested multinomial logit function (NMNL), use equation 8 to estimate β . Use the β values to estimate η_t in equation 10. Finally, with η_t we can estimate ξ from equation 9.

Appendix B: Drug data and Multicollinearity

This is not meant to be a general discussion of multicollinearity since this can be found in any econometrics texbook. Rather, this a discusion of why the data in this paper may be more prone to multicollinearity than data from other industries, say, computers. Multicollinearity occurs when explanatory variables are approximately linearly related. This results in very large variances for the OLS estimates. It may even result in unpredictable estimates, sometimes even reversing the signs of coefficients (Ramanathan, 1989).

Drug characteristics panel data may be more prone to multicollinearity for two reasons: 1) the performance characteristics of any one drug normally don't change over the years, and 2) each drug is normally sold in different presentations: The problem arising from this perculiarity is best illustrated by the table below:

Drug	Year	Present ation	Price	LDL-C (%)	TOTAL -C (%)	Trigly cerides (%)	HDL (%)	LDL/ HDL (%)	TOTAL-C /HDL (%)
Lovastatin	1988	60/20	4.46	-34%	-26%	-15%	8%	-37%	-29%
		100/20	4.54	-34%	-26%	-15%	8%	-37%	-29%
	1989	60/20	4.27	-34%	-26%	-15%	8%	-37%	-29%
		100/20	4.35	-34%	-26%	-15%	8%	-37%	-29%
	1990	60/20	4.33	-34%	-26%	-15%	8%	-37%	-29%
		100/20	4.40	-34%	-26%	-15%	8%	-37%	-29%
		60/40	3.89	-34%	-26%	-15%	8%	-37%	-29%
	1991	60/20	4.38	-34%	-26%	-15%	8%	-37%	-29%
		100/20	4.46	-34%	-26%	-15%	8%	-37%	-29%
		60/40	3.95	-34%	-26%	-15%	8%	-37%	-29%

As the table shows, the performance characteristics of lovastatin (mevacor) have remained the same over the years 1988 to 1991. Only the price of each presentation has changed. The chances for such a matrix of characteristics and prices being linearly related are higher than if the characteristics changed from year to year and if each presentation had different characteristics. For computers, each presentation normally has different performance attributes.

Detection of multicollinearity is not easy. High correlation between explanatory variables may be a sufficient condition for multicollinearity; but it is not a necessary condition. Methods for detecting multicollinearity are listed in most

econometrics textbooks (see for example, Ramanathan, 1989; Pindyk, 1988). For this paper, tolerance values, provided by the SYSTAT computer program that was used for all the regressions in this paper, were used to screen for multicollinearity in all the regressions. The tolerance of an explanatory variable here is defined as one minus the squared multiple correlation between that variable and the remaining explanatory variables. If there is no correlation at all, the tolerance is one. If there is high correlation, as is the case here, the tolerances is close to zero.

Appendix C: References for Data collection:

AJC 1990 sept 18, 66(8) 44B-55B (EXCEL study)
AJC Nov 11, 1988 Suppl Page 35J. The Finish Multicenter Study
AJC Nov 11, 1988 Suppl Page 35J. The Finish Multicenter Study
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Appendix D: Glossary of some terms used in the paper

HDL (High density Lipoprotien). This the so-called good cholesterol because it helps mop the system of cholesterol released by dying membranes and takes the cholesterol back the liver where it can be used. The more a drug can raised the level of this variable, the better the drug. It is also measured in percentage reduction.

LDL-C (Low density lipoprotein cholesterol). This is the so-called bad cholesterol for the reasons outlined earlier. The more a drug reduces LDL-C, the better the drug is. It is usually measured in percentage of cholesterol reduced.

LDL-C to HDL ratio: Since the idea is to reduce LDL-C and raise HDL, this ratio can be a very good measure of the effectiveness of a cholesterol drug. It is also measured in percentages and the more negative, the better.

Total-C (Total plasma cholesterol). This is the total plasma cholesterol also measured in percentage reduced. As with LDL-C, the more a drug reduces Total-C, the better the drug is.

Total-C to HDL ratio: Just like the LDL-C to HDL ration, the more negative, the better.

Triglycerides: The lipoproteins that transport cholesterol normally also carry triglycerides with them to adipose tissue where they are hydrolyzed to liberate fatty acids for tissue use. An excess of it in plasma is bad and the more a drug can reduce them, the better the drug. It is also measured in percentage reduction.